REMARKS

1. Status of the Claims

Claim 1 has been amended such as to recite trisodium citrate instead of trisodium phosphate as inadvertantly filed with the last set of claims in response to the Office Action dated December 29, 2008. Claim 1 of the application as filed correctly recites trisodium citrate. Claim 2 has been amended to be consistent with the stabilizing formulation comprising trisodium citrate. No new matter has therefore been added.

The Amendments of Claims 1-19 proposed by the Examiner on pages 2-6 of the Office Action for clarity reasons have been adapted in the current set of claims.

Claim 15 has been cancelled, thereby obviating the Examiner's objection thereto.

Therefore, the claim amendments do not raise a new issue after Final rejection. Applicants request the entry of the claims and their consideration.

2. Claim rejections under 35 U.S.C. § 102

In the outstanding Office Action, the Examiner has rejected claims 1 and 14-18 as being anticipated by Branovic et al. (Applied Biochemistry and Biotechnology, vol. 69, 1998, pages 99-111). Applicant disagrees respectfully for the following reasons.

2.1. Branovic et al. does not teach or suggest the use of hydrophobic amino acid within the meaning of the invention

Applicant submits that Branovic et al. disclose an improved procedure for purifying Factor VIII comprising a double virus inactivation step. The reference discloses in particular that the

corresponding virus inactivation steps were actually tested on FVIII compositions resulting only from two different purification methods:

- method 1 which is described from page 101, line 20 to page 102, line 14, and
- method 2, which is described in Myers et al., Vox Sanguinis, 1991, 60: 141-147. A copy of which is attached hereto.

With respect to method (1), Branovic et al. unambiguously disclose, at page 102, lines 9-1, that when method 1 is used, the purified FVIII is conditioned in a composition containing 0.3M glycine, 0.005 M $CaCl_2$ $2H_2O$, and 0.044 M sucrose, pH 7.0, before being freeze-dried.

Similarly, with respect to method (2), Myers et al. unambiguously disclose, at page 143, left column, lines 6 to 9, that FVIII is re-dissolved after precipitation and before freeze-drying in the final buffer disclosed at page 142, left column, lines 23-25, i.e. in a buffer containing 0.02 M sodium citrate, 0.04 M glycine, 0.06M NaCl, 0.005M calcium chloride and 1.5% sucrose at pH 7.1.

Thus, both methods 1 and 2 disclosed in Branovic et al. for purifying Factor VIII make use of a stabilizer comprising glycine, as well as trisodium citrate.

Therefore, the issue is whether glycine can be classified as a hydrophobic amino acid.

One of skill in the art knows that the hydropathy index of an amino acid is a number representing the hydrophobic or hydrophilic properties of its side-chain. It was proposed in 1982 by Jack Kyte and Russell Doolittle[1]. See for example Wikipedia, at http://en.wikipedia.org/wiki/Hydropathy_index.

[1] This reference is the Kyte et al reference cited in the application at page 6, lines 26-30.

The hydropathy index gives information as to the hydrophilicity and hydrophobicity of an amino acid. In brief, the lower the hydropathy index the more hydrophilic the amino acid is, the higher the hydropathy index the more hydrophobic the amino acid is.

For example, those amino-acids indicated in the application as being part of the group of the "most hydrophobic acids" according to Kyte et al. comprise valine (V), phenylalanine (F), and preferably leucine (L) and isoleucine (I) or mixture thereof; see Specification page 7, lines 33-37. The hydropathy index of these four amino-acids is given below (table extracted from the wikipedia reference mentioned above):

Hydropathy Index for the twenty natural amino acids (Kyte and Doolittle)

A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
1.8	-4.5	-3.5	-3.5	2.5	-3.5	-3.5	-0.4	-3.2	4.5	3.8	-3.9	1.9	2.8	-1.6	-0.8	-0.7	-0.9	-1.3	4.2

V, F, L, I respectively have hydropathy indexes of 4.2, 2.8, 3.8, 4.5.
Glycine (G) has an hydropathy index of -0.4. Glycine is therefore rather hydrophilic. Glycine is not an hydrophobic amino acid within the meaning of the invention.

In view of the above, it is clear that glycine used in Branovic et al. is not an hydrophobic amino acid within the meaning of the present application.

Thus, Branovic et al. fail to disclose an hydrophobic amino acid, as well as any stabilizing composition comprising a hydrophobic amino acid.

2.2. Branovic et al. do not teach or suggest the use of arginine in the process.

Moreover and most importantly, Branovic et al. unambiguously fail to disclose arginine.

The present invention is directed to a process for obtaining cryoprecipitable proteins comprising a step of contacting a composition of cryprecipitable protein(s) of interest with a stabilizing and solubilizing formulation comprising a mixture of arginine, at least one hydrophobic amino acid and trisodium citrate (i.e. wherein each one of these has at least three components present).

As disclosed especially at page 6, lines 26 to 35 of the present application, it is the specific combination of arginine, with at least one hydrophobic amino acid and trisodium citrate, which provides the formulation of the invention with "a marked improvement of the solubilization of the freeze-dried forms (of the cryoprecipitable proteins) after the heat treatment of virus inactivation".

The Examiner's attention is directed to the examples section in the present application, especially table 7. Composition C5, which comprises arginine, isoleucine and citrate, brings a marked improvement over the compositions of C, C3 and C4.

Composition C, C3, C4 and C5 are disclosed in Example 3 of the application.

Composition C comprises citrate and glycine, and corresponds to the composition disclosed in Branovic et al.

Composition C3 comprises C and arginine only.

Composition C4 comprises C and isoleucine only (isoleucine is the hydrophobic amino acid).

Composition C5 is the composition of the invention, namely it comprises C and arginine and an hydrophobic amino acid, i.e. C5 comprises a mixture of arginine, at least one hydrophobic amino acid and trisodium phosphate.

The Results in table 7 are as follows:

Filterability is about the same for all compositions. Redissolution time is 10-20 minutes for Compositions C, C3 and C4, but is markedly reduced for Composition C5 (4 minutes only). The multimer amount is again high for Compositions C and C3, and very low for Composition C5 (3%). Similarly the turbidity (NTU units) is very low with Composition C5.

Similarly, good results for Composition C5 are shown in tables 5 & 6.

Hence, Branovic et al. unambiguously fail to disclose the use of arginine and a hydrophobic amino acid, whereas the inventors of the present invention have shown the benefits associated with the specific, synergistic combination of a mixture of arginine, at least one hydrophobic amino acid and trisodium citrate.

In view of these differences and improved results, Applicant submits that novelty and non-obviousness must be recognized for the claimed subject matter of the present invention.

Withdrawal of the corresponding rejection is respectfully requested.

3. Conclusion

Applicant believes the pending application is in condition for allowance. Such favorable action is requested.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant respectfully petitions for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $130.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____ 36,623

Leonard R. Svensson
Registration No.: 30,330
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant

Enclosures: Myers et al.
Kyte & Doolittle